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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,653	04/27/2001	Julia E. Richards	UM-06105	1588

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EXAMINER	
SOUAYA, JEHANNE E	

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,653	RICHARDS ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-5, 7-11 and 16 in Paper No. 9 is acknowledged. Claims 6, 12-15, and 17-23 have been canceled. The restriction requirement is therefore made FINAL. An action on the merits of claims 1-5, 7-11, and 16 follows.

Claim Rejections - 35 USC § 112

Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a nucleic acid comprising SEQ ID NO 1 or the complement of SEQ ID NO 1 or a nucleic acid encoding the polypeptide of SEQ ID NO 3 or the complement of such, said sequences operably linked to a heterologous promoter or contained within a vector, does not reasonably provide enablement for a composition comprising a nucleic acid sharing at least 96%, 97% or 98% identity with SEQ ID NO 1, a composition comprising a nucleic acid encoding a polypeptide that shares at least 96% or 97% or 98% identity with SEQ ID NO 3, complements of such, or these nucleic acid sequences operably linked to a heterologous promoter or contained in a vector. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to sequences comprising a nucleic acid sharing at least 96%, 97% or 98% identity with SEQ ID NO 1, a nucleic acid encoding a polypeptide that shares at least 96% or 97% or 98% identity with SEQ ID NO 3 and complements of such. The claims broadly encompass allelic variants, mutants and homologs of SEQ ID NO 1 that have not been taught or described in the specification. The specification teaches the nucleic acid sequence of SEQ ID NO 1 as well as the polypeptide sequence of SEQ ID NO 3 (LPH3, latrophilin 3). The specification further teaches (p. 4, 6, 30, and 37-39) that variants and mutants are encompassed by the invention and that they can be generated by mutagenizing the nucleic acid sequence and screening the resulting variants for LPH3 activity. The specification teaches that mutants include those that have enhancing therapeutic or prophylactic efficacy or stability (p. 37, line 4), that variants include those that have a greater affinity for the TIGR peptide (p. 37, lines 8-9), and that homologs include those that have intracellular half lives dramatically different that the corresponding wildtype protein (p. 37, lines 24-25). With regard to such activities, the specification speculates that LPH3 binds the TIGR peptide however the specification does not demonstrate or provide any examples that LPH3 (the peptide of SEQ ID NO 3) actually binds the TIGR peptide. Further, the specification does not demonstrate any therapeutic or prophylactic activity for SEQ ID NO 3 nor does the specification teach the intracellular half life of SEQ ID NO 3. In addition, the specification does not teach what amino acids would be involved in the

binding of LPH3 to TIGR or in any other activity of LPH3. Without such knowledge, the skilled artisan would not be able to establish a predictable correlation between mutagenizing specific amino acids of SEQ ID NO 3 and the result on any activity of LPH3 without extensive trial and error analysis. The results of such analysis are unpredictable as it is well known in the art that changing a single amino acid can change the activity of a polypeptide (see Proudfoot et al, Journal of Biological Chemistry, vol. 271, pp 2599-2603, which teaches that extension of recombinant human RANTES by a single residue [Met-RANTES] at the amino terminus was sufficient to produce a potent and selective antagonist - see abstract) and that some of these changes are unpredictable. When the activity of a specific protein is unknown, such analysis is further unpredictable because no correlation has been established between specific amino acids and the function or activity of the polypeptide.

The art does not teach the activity of LPH3. While Matsushita et al (FEBS Letters, vol. 443, pp 348-352, 1999) teaches that latrophilins are unusual GPCRs (G Protein Coupled Receptor), Matsushita also teaches that multiple alternative splicing makes the proteins highly variable and that the differential tissue distribution of latrophilins and the ability of only LPH1 (bovine) to bind LTX (α-latrotoxin) suggest that each member of the family of receptors has distinct functions) (see p. 348, col 2, lines 2-7). Thus the art teaches that even comparing LPH3 to others in the same family does not give the skilled artisan any predictable correlation between the ligands bound by members of the family (see p. 352, col 1) and that future work must concentrate on the functions of the receptors and their endogenous ligands.

Thus, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. The analysis required to make and use the claimed nucleic acids requires that the skilled artisan first establish the activity of SEQ ID NO 3, which neither the specification nor the art demonstrate, and then mutate each and every position with conservative and nonconservative substitutions (contemplated by the specification) and test the result of such mutations on the activity of LPH3. The specification teaches polymorphisms in LPH3 that lead to single amino acid changes, (see p. 90), however the specification falls short of enabling the skilled artisan of how to use the broadly claimed invention because it does not taught the effect of these substitutions on the activity if LPH3, nor if they are associated with glaucoma and instead asserts that an analysis should be done to determine if the polymorphisms co segregate with a disease phenotype. The information provided in the specification is an invitation for further study and this analysis is in effect a research project and requires extensive trial and error manipulations with unpredictable results, which is considered undue experimentation.

Written Description

4. Claims 1-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to sequences comprising a nucleic acid sharing at least 96%, 97% or 98% identity with SEQ ID NO 1, a nucleic acid encoding a polypeptide that shares at least 96% or 97% or 98% identity with SEQ ID NO 3 and complements of such. The claims broadly encompass a genus of polynucleotides that includes allelic variants, mutants and homologs of SEQ ID NO 1 that have not been taught or described in the specification. The specification teaches the nucleic acid sequence of SEQ ID NO 1 as well as the polypeptide sequence of SEQ ID NO 3 (LPH3, latrophilin 3) and such sequences fulfill the written description requirement of 35 USC 112, first paragraph. The specification further teaches (p. 4, 6, 30, and 37-39), however, that variants and mutants are encompassed by the invention, and that mutants include those that have enhancing therapeutic or prophylactic efficacy or stability (p. 37, line 4), that variants include those that have a greater affinity for the TIGR peptide (p. 37, lines 8-9), and that homologs include those that have intracellular half lives dramatically different that the corresponding wildtype protein (p. 37, lines 24-25). With regard to such activities, the specification speculates that LPH3 binds the TIGR peptide however the specification does not demonstrate or provide any examples that LPH3 (the peptide of SEQ ID NO 3) actually binds the TIGR peptide. Further, the specification does not demonstrate any therapeutic or prophylactic activity for SEQ ID NO 3 nor does the specification teach the intracellular half life of SEQ ID NO 3. In addition, the specification does not teach or describe what amino acids would be involved in the binding of LPH3 to TIGR or in any other activity of LPH3. Without such knowledge, the skilled artisan would not be able to establish a predictable correlation between

mutagenizing specific amino acids of SEQ ID NO 3 and the result on any activity of LPH3 without extensive trial and error analysis.

Therefore, the recitation of SEQ ID NO 1 and the rat and bovine homologs taught in the specification is not representative of the large genus of mutants, variants, and homologs that the specification asserts are encompassed by the broadly claimed invention. Although the specification sets forth 5 amino acid substitutions in LPH3 (see p. 90), the specification does not teach whether such are associated with aberrant, enhanced, or normal biological activity of SEQ ID NO 3, and thus the specification is deficient in describing a representative number of mutants and variants with altered, retained or enhance activity or homologs with dramatically different half lives.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the nucleic acid of SEQ ID NOS: 1 and a nucleic acid sequence encoded by SEQ ID NO 3, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it

is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

It is noted that because the nucleic acids encompassed by claims 1-3 and 7-9 lack sufficient written description, that sequences linked to such and vectors containing such also lack adequate written description. Accordingly, the specification does not provide a written description of the invention of claims 1-5 and 7-11.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AF111095 (March 4, 1999).

Accession number AF111095 (sequence alignment provided) teaches a nucleic acid that encodes a polypeptide that has 96.785% sequence identity with the polypeptide of SEQ ID NO 3. It is noted that the "composition" of claim 7 has been given no patentable weight has it provides no added structure to the sequence itself. The "composition" of claim 7 could be the nucleic acid itself.

Conclusion

7. The sequence of SEQ ID NO 1 is free of the prior art. Claim 16 is allowable over the cited prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
August 8, 2002